Brief Communication

Polymyositis–Dermatomyositis-associated Interstitial Lung Disease

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We report findings in 70 patients with both diffuse interstitial lung disease and either polymyositis (PM) or dermatomyositis (DM). Initial presentations were most commonly either musculoskeletal (arthralgias, myalgias, and weakness) or pulmonary (cough, dyspnea, and fever) symptoms alone; in only 15 patients (21.4%) did both occur simultaneously. Pulmonary disease usually took the form of acute to subacute antibiotic-resistant community-acquired pneumonia. Chest radiographs and computed tomography most commonly demonstrated bilateral irregular linear opacities involving the lung bases; occasionally consolidation was present. Jo-1 antibody was present in 19 (38%) of 50 patients tested. Synchronous associated malignancy was present in 4 of 70 patients (5.7%). Surgical lung biopsies disclosed nonspecific interstitial pneumonia (NSIP) in 18 of 22 patients (81.8%), organizing diffuse alveolar damage (DAD) in 2, bronchiolitis obliterans organizing pneumonia (BOOP) in 1, and usual interstitial pneumonia (UIP) in 1. Treatment usually included prednisone in 40–60 mg/d dosages for initial control, followed by lower dose prednisone plus an immunosuppressive agent such as azathioprine or methotrexate for disease suppression. Survival was significantly better than that observed for historical control subjects with idiopathic UIP, and was more consistent with survival previously reported in idiopathic NSIP. There was no difference in survival between Jo-1 positive and Jo-1 negative groups.

Keywords: polymyositis–dermatomyositis; interstitial lung disease; survival; azathioprine; prednisone

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders that may be associated with diffuse interstitial lung disease (ILD). The frequency of ILD in PM–DM has been reported to range between 5 and 30% depending on the diagnostic method (1, 2).

Early descriptions of the ILD associated with PM–DM suggested that it shared many features with idiopathic pulmonary fibrosis (IPF) (3, 4), although some patients had histological findings described as diffuse alveolar damage (DAD), bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia (UIP), or a nonclassifiable interstitial pneumonia (5, 6). Because there have been some changes in the classification of the idiopathic interstitial pneumonias, this retrospective study was done to characterize the clinical, radiographic, and histological features of the ILD associated with PM and DM seen at a large referral institution in a large consecutive cohort of patients using the new interstitial pneumonia classification. We also attempted to determine whether patient outcomes differ from those with similar ILDs not associated with PM–DM.

METHODS

Patient Selection

A computer-aided search was conducted to identify all patients seen at the Mayo Clinic Rochester (MCR) during the time period from January 1, 1990 to December 31, 1998 with records coded with diagnoses dermatomyositis, polymyositis, overlap syndrome, or undifferentiated connective tissue disease plus either pulmonary fibrosis or interstitial pneumonia.

Diagnostic Criteria

Criteria for a diagnosis of polymyositis–dermatomyositis were those described by Bohan and Peter (7), including symmetric proximal muscle weakness with or without dysphagia or respiratory muscle weakness, muscle enzyme elevations, electromyographic abnormalities, compatible muscle biopsy, and/or skin rash of dermatomyositis. Patients with undifferentiated connective tissue disease were included only when active myopathy was present and when the connective tissue disorder was not predominantly progressive systemic sclerosis or systemic lupus erythematosus. The presence of diffuse parenchymal lung disease by chest radiograph was required for inclusion. Patients with single episodes of antibiotic-responsive community-acquired pneumonia and those with other infections of the lung were excluded. Patients less than 18 yr of age were also excluded.

Clinical and Laboratory Test Results

Clinical data and test results were abstracted from the clinical record, which included the clinical history, physical examination, laboratory test results, radiographic findings, biopsy results, and electromyography (EMG). Presenting signs and symptoms were recorded from the first MCR encounter, which eventually led to a diagnosis of both ILD and PM–DM. Pulmonary function tests were performed using Medical Graphics equipment and are expressed as percent of predicted values, using previously described criteria (8).

Chest Radiographs and Computed Tomography of the Chest

Chest radiographs and computed tomograms (CT) of the lungs were reviewed and interpreted without knowledge of biopsy results or clinical manifestations by two radiologists with an interest in thoracic imaging (T.E.H., R.P.H.). Chest radiographs and CT scans were scored by consensus for pattern, distribution, and extent of involvement.

Lung Biopsy

Surgical lung biopsies were categorized (H.D.T.) without knowledge of clinical or radiological information, using the classification described by Katzenstein and Myers (9).

Data Analysis

Data are presented using mean ± SD for continuous variables and percentages for categorical variables. Survival following diagnosis of

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ILD was performed for patients whose initial diagnosis of ILD or PM–DM occurred during the study period or within 1 mo prior to the start of the study period. For patients who were diagnosed with PM–DM prior to a diagnosis of ILD, time zero was defined as the date of the first abnormal chest radiograph at MCR following the diagnosis of PM–DM. Cumulative survival probabilities were estimated using the Kaplan–Meier method. The log-rank test was used to compare survival of groups of patients. In all cases two-sided tests were used with p values <0.05 used to denote clinical significance. The survival curve for PM–DM-ILD was compared with curves previously published from this institution (10) that were derived from patients undergoing surgical lung biopsy for pulmonary fibrosis. These biopsies were recently reclassified into subsets including UIP and NSIP using the system described by Katzenstein and Myers (9).

RESULTS

Clinical Features

During the study period, 973 patients were diagnosed at Mayo Clinic Rochester (MCR) with PM–DM. In addition, 3363 other patients were diagnosed with unclassified or mixed connective tissue disease. Within these groups, 221 were also coded as having pneumonia, and 244 others as having pulmonary fibrosis. From a review of these records, 70 patients met our clinical and radiographic inclusion criteria. Of these 70 patients, 58 were first diagnosed with PM–DM or ILD during the study period or within 30 d prior to the start of the study period. The remaining 12 patients were first diagnosed a median of 4.53 yr (range 1.23 to 11.55 yr) prior to the start of the study period. Patient demographics and symptoms and signs recorded at the initial presentation to Mayo Clinic Rochester MCR are summarized in Table 1.

The majority of those with pulmonary symptoms had what appeared to be persistent community-acquired pneumonia refractory to antibiotic therapy. One patient presented with the acute respiratory distress syndrome requiring endotracheal intubation and mechanical ventilation. At the time of the initial diagnosis, seven patients complained of dysphagia, but only one patient had good evidence for recurrent aspiration of food or gastric contents. Muscle weakness was noted in about one-half of patients at the time of diagnosis but only one patient had progressive muscular weakness of sufficient severity to require mechanical ventilation of the lungs.

TABLE 1. CLINICAL AND LABORATORY FINDINGS

Clinical Findings		n	%
Female		37	52.9
Age, yrs ± SD	52.6 ± 14.1		
Smoking history			
Never		37	52.9
Former		31	44.3
Current		1	1.4
Not recorded		1	1.4
Initial symptom(s)			
Musculoskeletal (myalgias, arthralgias, weakness)		25	35.7
Pulmonary (cough, dyspnea, fever)		21	30.0
Pulmonary and musculoskeletal together		15	21.4
Rash alone		4	5.7
Other (Raynaud's, etc.)		3	4.2
Symptoms and signs present at the time of diagnosis at Mayo Clinic Rochester			
Crackles on auscultation of lungs		59	84.3
Weakness		36	51.4
Arthralgias or arthritis		31	44.3
Raynaud's phenomenon		14	20.0
Rash		8	11.4
Dysphagia		7	10.0
Laboratory Tests	**Number Positive/ Number Tested**		**%**
Blood tests			
Lactic dehydrogenase (LDH)	29/34		85.3
Aspartate aminotransferase (AST)	57/68		83.8
Aldolase	23/29		79.3
Creatine phosphokinase (CPK)	50/64		78.1
Erythrocyte sedimentation rate > 30 mm/h	31/69		44.9
Antinuclear antibodies (ANA)	27/67		40.3
Anti-Jo-1 antibody	19/50		38.0
Myopathy present by electromyography	49/53		92.5
Skeletal muscle biopsy			
Myopathy present	45/52		86.6
Inflammatory myopathy apparent	18/52		34.6
Myopathy and atrophy together	11/52		21.2

Laboratory Findings

Laboratory findings are summarized in Table 2, including selected blood tests, EMG, and skeletal muscle biopsy results. Serum creatine phosphokinase and aldolase levels were elevated in most patients.Electromyography was done at MCR in 53 patients and showed active myopathy in 49, normal findings in 3, and was indeterminate in 1. Skeletal muscle biopsy was available for review in 52 patients, and myopathy was present in 45. Five biopsies were nondiagnostic and 2 others showed atrophy only. Skin biopsies were done in 22 patients and usually were interpreted as demonstrating evidence of chronic dermatitis without specific features.

Chest Radiographs and Computed Tomography of the Chest

Chest radiographs were available for review in 57 patients and chest computed tomograms were available for review in 30 patients. Predominant findings are summarized in Table 2. Irregular linear opacities with bilateral and lower lung predominance were the most common finding by chest radiography and CT of the chest.

Surgical Lung Biopsies

Surgical lung biopsies were available for 22 patients. The histological diagnosis was cellular nonspecific interstitial pneumonia (NSIP) in 7, combined cellular and fibrotic NSIP in 9, fibrotic NSIP in 2, UIP in 1, acute and organizing DAD in 2, and BOOP in 1. Thus, using the classification scheme described by Katzenstein and Myers (9), findings consistent with NSIP were found in 18 of 22 (81.8%) of the surgical lung biopsies.

Pulmonary Function

Impairment of pulmonary function was predominantly restrictive, with total lung capacity 67.6 ± 14.0% (mean ± SD) predicted, and was below 80% of the predicted value in 27 of 33

TABLE 2. IMAGING FINDINGS

Finding	Frequency	Bilateral (%)	Lower Lobe Predominant (%)
Chest radiographs			
Irregular linear opacities	54/57 (95%)	98	93
Consolidation	14/57 (25%)	79	100
Honeycombing	2/57 (4%)	100	100
Pleural effusion	2/57 (4%)	50	NA*
Computed tomography of the lungs			
Irregular linear opacities	19/30 (63%)	100	68
Consolidation	16/30 (53%)	100	81
Ground glass opacities	13/30 (43%)	100	31
Pleural effusion	6/30 (20%)	67	NA
Honeycombing	0/30 (0%)	NA	NA

* NA = not applicable or meaningful.

patients tested. Forced vital capacity was 63.7 ± 16.0% predicted and was below 80% predicted in 31 of 38 of those tested. Single-breath diffusing capacity of the lungs was 55.9 ± 15.2% predicted and was below 80% predicted in 35 of 37 of those tested.

Treatment

The initial treatment in 67 (95.7%) of the 70 patients included corticosteroids, usually in the form of oral prednisone (most commonly 40–60 mg/d), occasionally as hydrocortisone or an equivalent agent administered intravenously. Other agents were often added as steroid sparing agents or antifibrotic agents, usually later in the course, often because of a lack of favorable response to treatment of either the inflammatory myopathy or the interstitial lung disease or both. These drugs included azathioprine in 25, methotrexate in 14, cyclophosphamide in 7, cyclosporin in 3, intravenous immunoglobulin in 2, colchicine in 15, hydroxychloroquine in 10, and sulfa drugs in 6.

Survival

The survival curve for the group of 58 patients whose PM–DM-ILD was first diagnosed in 1990 or later is shown in Figure 1. Mean age for this subset was 52.7 ± 14.4 (mean ± SD) yr, and 28 (48.3%) were female. One-year survival was 85.8%, 3-yr survival was 74.4%, and 5-yr survival was 60.4%. The cause of death was known in 11 of 18 patients and included progressive ILD (6 patients), superimposed pneumonia (4 patients), and lung cancer (1 patient). Survival was not significantly different ($p = 0.247$) for these 58 PM–DM-ILD patients than for 14 historical control patients with biopsy-proven idiopathic NSIP (10), but was significantly better ($p < 0.001$) when compared with 63 historical control patients with biopsy-proven IPF–UIP (10) (Figure 1). Survival for the 19 Jo-1 positive patients was not different ($p = 0.585$) than that for the 28 Jo-1 negative patients (Figure 2). For the 16 PM–DM patients in this study who had NSIP on biopsy and who also met our criteria for inclusion in the survival analysis, survival was virtually identical ($p = 0.871$) to the 14 patients with idiopathic NSIP reported in the study of Bjoraker and coworkers (10).

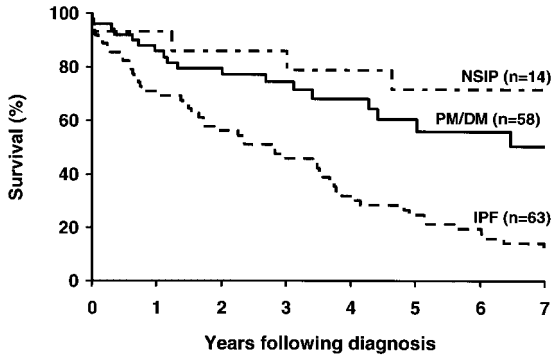

Figure 1. Overall survival for 58 patients with polymyositis or dermatomyositis and associated interstitial lung disease (PM–DM-ILD), compared with 63 historical control patients with biopsy-proven idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF) and 14 patients with biopsy-proven idiopathic nonspecific interstitial pneumonia (NSIP). We included only those patients whose initial diagnosis of diffuse lung disease was made by chest radiography at Mayo Clinic Rochester within 1 mo of the start of the study period. One-year survival for patients with PM–DM-ILD was 85.8%, 3-yr survival was 74.7%, and 5-yr survival was 60.4%. Survival is better ($p < 0.001$) for the PM–DM-ILD group when compared with the group with IPF, and is not different from the group with idiopathic NSIP ($p = 0.247$).

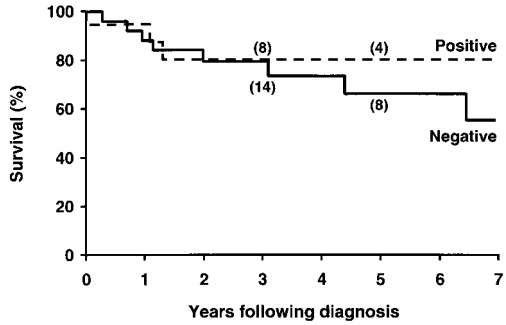

Figure 2. Survival of 19 Jo-1 positive patients compared with 28 Jo-1 negative patients with PM–DM-ILD. There is no difference between groups ($p = 0.585$). Number in parentheses represents number of patients at risk for the corresponding year.

Associated Malignancy

Three patients had malignancies synchronous with the diagnosis of PM–DM-ILD, including one each with adenocarcinoma of the breast, hypernephroma of the kidney, and malignant degeneration in a hidradenoma. One patient had primary bronchogenic carcinoma related to long-standing IPF, with dermatomyositis complicating the malignancy.

DISCUSSION

We conclude that the interstitial lung disease associated with PM–DM usually takes the form of NSIP with characteristic histopathology, radiographic findings, responsiveness to therapy, and survival. Occasionally, the disease may present as acute interstitial pneumonia with DAD with rapid progression to respiratory failure or BOOP. Recurrent aspiration pneumonia due to esophageal involvement and ventilatory failure due to muscle weakness were not commonly associated with diffuse lung disease in our series.

Prior studies describing the histopathology of ILD in PM–DM have recognized several patterns including DAD, BOOP, cellular interstitial pneumonia (not otherwise specified), and UIP (5, 6). Only one patient in the current series had a diagnosis of BOOP, perhaps in part reflecting our exclusion of the histopathology of patients diagnosed by clinical criteria plus transbronchial lung biopsy without confirmatory surgical lung biopsy. Patients previously diagnosed as having cellular interstitial pneumonia are now usually described as having cellular NSIP, and some patients now said to have fibrotic NSIP probably include patients formerly diagnosed as having UIP. Using the current classification scheme and terminology (9) the majority of the surgically biopsied patients in this study (81.8%) had NSIP.

The better survival associated with NSIP (10–14) undoubtedly accounts for the better survival reported for patients with PM–DM-ILD in comparison with patients with classic IPF. Furthermore, survival was more consistent with that previously reported for either idiopathic NSIP (10–14) or idiopathic BOOP (14) than for IPF (10, 13–15). Responsiveness to corticosteroid therapy with or without immunosuppressive agents also was more consistent with the results reported for NSIP than for IPF (10–15).

Thirty percent of our patients presented with diffuse lung disease without obvious signs or symptoms of PM–DM. Treatment with corticosteroids for idiopathic organizing pneumonia or NSIP characteristically suppressed the PM–DM and in some cases obscured or delayed the diagnosis for weeks to years after the initial presentation. Although considerable ef-

forts were made to identify all patients with PM–DM-ILD during the study period, it is probable that some patients with this disease at MCR went unrecognized.

The most common CT findings in lung disease associated with PM–DM have been irregular linear opacities with areas of consolidation and ground-glass attenuation (16–18). Honeycombing has not been a common finding in these patients, with one study by Mino and coworkers (17) showing no honeycombing in 17 cases and honeycombing having been seen in only 2 of 7 patients reported by Akira and coworkers (18). Our results correlate well with these previous studies in that irregular linear opacities with bilateral and lower lung predominance were the most common finding, and consolidation was the next most frequent pattern. In these studies, consolidation often resolved on serial CT and was found to be correlated with histologic findings of BOOP.

The irregular linear opacity pattern likely corresponds to the histological finding of NSIP in the current group of patients. The relative absence of honeycombing is also in keeping with the histological diagnosis of NSIP. Although honeycombing has been reported in NSIP (16), it is a less prominent finding than is typically seen in IPF–UIP, where it can be seen in up to 90% of patients (15).

The optimal treatment program for patients with interstitial lung disease associated with PM–DM is not known. For the induction of remission, we have favored prednisone, usually with steroid-sparing agents. Prednisone in the 60 mg/d range seems effective in suppressing the PM–DM within a few weeks in most patients, but may lead to complicating steroid myopathy if continued at high doses. Therefore, gradual tapering of the steroid dose is important, with careful monitoring of creatine phosphokinase, chest radiographs, and pulmonary function. The lung disease usually is slower to respond to therapy than is the PM–DM, and may require treatment over several months. Pulse intravenous cyclophosphamide has been reported to induce an initial remission of lung disease (19, 20), but was not employed in this series. Incomplete resolution of pulmonary infiltrates with residual bibasilar linear opacities is commonly observed.

The ideal steroid-sparing regimen for maintenance of remission is unknown. We most frequently used azathioprine (21, 22) or methotrexate, usually preferring the former because of the potential for methotrexate-induced diffuse interstitial lung disease. Hydroxychloroquine was often also added as a steroid-sparing agent, and in at least one patient was the only drug used during a period of remission lasting several years. Colchicine was used as a potentially antifibrotic drug during this period, but has not been proven to be effective in treating the IPF (8). Intravenous immunoglobulin was added to failing regimens on two occasions and did not alter the outcome. Others have reported success in treating Jo-1 positive ILD with a combination of prednisone, cyclosporine, and azathioprine, each used in low dosage (23), in a regimen similar to that currently used for prevention of rejection after solid organ transplantation.

In summary, most patients with PM–DM-ILD appear to have histopathological findings of NSIP, which is associated with a better prognosis and response to corticosteroid therapy than those seen in patients with IPF. Although a positive Jo-1 antibody result may point to underlying PM–DM, it does not appear to have prognostic value.

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References

1. Schwarz MI. Pulmonary and cardiac manifestations of polymyositis-dermatomyositis. *J Thorac Imag* 1992;7:46–54.
2. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. *J Thorac Imag* 1996;11:250–259.
3. Dickey BF, Myers AR. Pulmonary disease in polymyositis-dermatomyositis. *Semin Arth Rheum* 1984;14:60–76.
4. Duncan PE, Griffin JP, Garcia A, Kaplan SB. Fibrosing alveolitis in polymyositis: a review of histologically confirmed cases. *Am J Med* 1974; 57:621–626.
5. Schwarz MI, Matthay RA, Sahn SA, Stanford RE, Marmorstein BL, Scheinhorn DJ. Interstitial lung disease in polymyositis and dermatomyositis: analysis of six cases and review of the literature. *Medicine* 1976;55:89–104.
6. Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV. Interstitial lung disease in polymyositis and dermatomyositis. *Am Rev Respir Dis* 1990;141:727–733.
7. Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;292:344–347; 403–407.
8. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: impact of oxygen and colchicine, prednisone or no therapy on survival. *Am J Respir Crit Care Med* 2000;161:1172–1178.
9. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis. Clinical relevance of pathological classification. *Am J Respir Crit Care Med* 1998; 157:1301–1315.
10. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DA, Offord KP. Prognostic significance of histopathological subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157: 199–203.
11. Katzenstein AA, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histological features and clinical significance. *Am J Surg Pathol* 1994;18:136–147.
12. Nicholson AG, Colby TV, DuBois RM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000;162:2213–2217.
13. Daniil ZD, Gilchrist FC, Nicholson AG, Hansell DM, Harris J, Colby TV, DuBois RM. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1999;160:899–905.
14. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. *Eur Respir J* 1998;12:1010–1019.
15. American Thoracic Society International Consensus Statement. Idiopathic pulmonary fibrosis: diagnosis and treatment. *Am J Respir Crit Care Med* 2000;161:646–664.
16. Hartman TE, Swensen SJ, Hansell DM, Colby TV, Myers JL, Tazelaar HD, Nicholson AG, Wells AU, Ryu JH, Midthun DE, *et al*. Nonspecific interstitial pneumonia: variable appearance at high-resolution chest CT. *Radiology* 2000;217:701–705.
17. Mino M, Noma S, Taguchi Y, Tomii K, Kohri Y, Oida K. Pulmonary involvement in polymyositis and dermatomyositis: sequential evaluation with CT. *AJR* 1997;169:83–87.
18. Akira M, Hara H, Sakatani M. Interstitial lung disease in association with polymyositits-dermatomyositis: long-term follow-up CT evaluation in seven patients. *Radiology* 1999;210:333–338.
19. Schnabel A, Reuter M, Gross WL. Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular disease. *Arth Rheum* 1998;41:1215–1220.
20. Shinohara T, Hidaka T, Matsuki Y, Ishizuka T, Takamizawa M, Kawakami M, Kikuma H, Suzuki K, Nakamura H. Rapidly progressive interstitial lung disease associated with dermatomyositis responding to intravenous cyclophosphamide pulse therapy. *Intern Med* 1997; 36:519–523.
21. Bunch TW, Worthington JW, Combs JJ, Ilstrup DM, Engel AG. Azathioprine and prednisone for polymyositis: a controlled clinical trial. *Ann Intern Med* 1980;92:365–369.
22. Bunch TW. Prednisone and azathioprine for polymyositis: long-term follow-up. *Arth Rheum* 1981;24:45–48.
23. Sauty A, Rochat T, Schoch OD, Hamacher J, Kurt AM, Dayer JM, Nicod LP. Pulmonary fibrosis with predominant CD8 lymphocytic alveolitis and anti-Jo-1 antibodies. *Eur Respir J* 1997;10:2907–2912.